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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/732,862	12/10/2003	Katelynne Lyons	ICC-136.0 (4564/88881)	9117

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EXAMINER	
PENG, BO	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 11/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/732,862	LYONS ET AL.	
	Examiner	Art Unit	
	Bo Peng	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/21/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 29, 2006 has been entered.

2. Claims 1-46 are pending and considered in this Office action.

3. The rejection of Claims 1-46 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is **withdrawn**.

4. The rejection of Claim 25 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is **withdrawn** in view of amendment.

5. The rejection of Claims 1-46 under 35 U.S.C. § 112, first paragraph, **is withdrawn** in view of amendment.

6. The rejection of Claim 25 under 35 U.S.C 102(b), as being anticipated by Zlotnick (1997), **is withdrawn** in view of Applicant's amendment.

7. The rejection of Claims 25, 27-28, 30, 32 and 43-46 under 35 U.S.C 102(a), as being anticipated by Jegerlehner, **is withdrawn** in view of Applicant's amendment.

8. The rejection of Claims 2, 4-6, 16-22, 30-39 and 43-46 under 35 U.S.C. §103, as being obvious over Zlotnick *et al.* (1997) and further in view of Pumpens (1995), **is withdrawn** in view of Applicant's amendment.

9. The rejection of Claims 2, 17, 30 and 31 under 35 U.S.C. 103(a), as being unpatentable over Nierynck et al. (1998) and Zlotnick et al (1997), **is withdrawn** in view of Applicants' amendment.

10. The rejection of Claims 1-46 under the judicially created doctrine of obviousness-type double patenting, as being unpatentable over (1) claims 1-78 of 09/930,915; (2) Claims 1-53 of 10/787,734; (3) Claims 98-109 of 10/805,913 and Claims 79-115 of 10/806,006, **is maintained**. Applicant acknowledges the rejection and does not wish to prematurely respond.

11. The following are new rejections:

Claim Rejections - 35 USC § 112, first paragraph

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 1-46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection affects all dependent claims.

14. Please note that the newly amended scope of "said chimer molecule containing up to about 5 ~~20~~ percent conservatively substituted amino acid residues in the HBc sequence relative to SEQ ID NO: 1," in Claims 1, 11 and 25 is NEW MATTER. While the conservatively substitution of amino acids of epitops and native cystines is described in paragraphs [0081], [0231] and [0393] of the specificatiojn, no description of "5 percent conservatively substituted amino acid residues in the HBc sequence relative to SEQ ID NO:1" is found in the specification.

15. Removal of all new matter is required. *In re Russsmussen* 210 USPQ 325.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. Claims 1-6, 8-14, 16-28, 30-42 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pumpens et al. (1995, Intervirology, Vol. 33, pp. 63-74), in view of Zlotnick, et al. (1997, PNAS, Vol. 94, pp. 9556-9561) and Zhang (1992, J. Biological Chemistry, Vol. 267 (13): pp. 9922-9429).

18. Claims 1-6, 8-14, 16-28, 30-42 and 46 are directed to a recombinant chimer hepatitis B core (HBc) protein molecule up to about 380, or up to 600 amino acid residues in length that (a) contains at least about 125 of the N-terminal of HBc, which includes the HBc sequence of residue positions 4 through about 75 and about 85 through about 140 in which one or both cysteine residues at positions 48 and 107 is replaced by another residue, and in which the cysteine at residue position 61 is present; wherein the residue substituted for each cysteine at positions 48 and 107 is individually selected from the group consisting of glutamine, asparagine, serine, alanine, threonine and lysine; (b) optionally contains a peptide-bonded heterologous amino acid residue sequence at one or more of the N-terminus, between residue positions about 76 through about 85 (in the HBc immunodominant loop) or the C-terminus of the chimer, and wherein (i) zero to all residues in a sequence in said HBc immunodominant loop are present or replaced and peptide-bonded to one to about 245 amino acid residues of said heterologous amino acid residue sequence that constitutes an immunogen or a sequence of up to about 40 residues that constitutes an anti-antigen or a chemically-reactive linker residue for a conjugated hapten or (ii) the sequence of HBc at positions 76 through 85 is present and free from deletions and heterologous residues or (iii) one or more of residues 76 through 85 is absent or replaced, (c) contains one or both of (i) one to three cysteine residues at an amino acid position of the chimer molecule corresponding to amino acid position -20 to about +1 from the N-terminus of the HBc sequence of SEQ ID NO:1 [N-terminal cysteine residue(s)] in a sequence other than that of the HBc precore sequence and (ii) one to three cysteine residues toward the C-terminus of the molecule from the C-terminal residue of the HBC sequence and within about 30 residues from the C-terminus of the chimer molecule [C-terminal cysteine residue(s)]; said chimer molecule (i)

containing up to about 5 percent conservatively substituted amino acid residues in the HBc sequence, (ii) self-assembling into particles that are substantially free of binding to nucleic acids after expression (Claims 1, 11-14, 24, 25, 30 and 46), wherein the N-terminal sequence of the recombinant chimer hepatitis B core protein molecule includes a heterologous sequence containing up to about 75 amino acid residues peptide-bonded to one of HBc residues 2-4 that includes an immunogenic epitope (Claims 2, 16, 17 and 31), wherein zero to all residues in a sequence of HBc positions 76 through 85 are present and peptide-bonded heterologous epitope (Claim 4), wherein one or more of residues 76 through 85 is absent or replaced (Claim 5), wherein the C-terminal sequence contains up to about 100 amino acid residues that include an immunogenic epitope in a sequence heterologous to HBc and bonded to said C-terminal residue of the HBc sequence (Claims 6, 19 and 33), wherein a second peptide-bonded sequence (B or T cell eptope) of up to about 75 residues present bonded to the N-terminus, in immunodominant loop or to the C-terminus of the chimer (Claims 20-22 and 34-39), wherein an HBc sequence is at least about 125 of the N-terminal 163 amino acid residues of the HBc molecule (Claims 8, 23 and 24), wherein the recombinant chimer hepatitis B core protein molecule is up to about 380 amino acid residues in length, wherein the recombinant chimer hepatitis B core protein molecule contains at least about 135 of the N-terminal 163 amino acid residues of HBc (Claims 10, 27 and 28), wherein said chimer contains the uninterrupted HBc amino acid residue sequence of position 4 through position 149, plus a cycteine residue at the C-terminus (Claims 41 and 42).

19. Pumpens (1995) teaches immunogenic compositions and vaccines using recombinant HBc chimer molecules of a variety of lengths up to about 380 or 600 amino acid residues in length. Pumpens teaches that both full-length HBc and C-terminal truncated HBcΔ can form

capsid particles. The HBc and HBcΔ chimers can carry B-cell and T-cell epitopes at their N-terminal, C-terminal or at internal immunodominant loop sites at positions 76 through 85 (See Figure 1 and Tables 1 through 3). Pumpens also teaches such chimers can contain two epitopes at both the immunodominant loop and C-terminal (see Table 2). These chimers contain an HBc sequence of at least about 130 of the N-terminal 150 amino acid residues of the HBc molecule (See for instance Fig. 1, pg. 64) that include a peptide-bonded heterologous epitope (Table 1, page 66) or a heterologous linker residue which code for epitope present in the HBc immunodominant loop at positions 76 through 85 (see page 69, col. 1, last paragraph). Pumpens discloses that HBc chimeras with C-terminal truncations are capable of self-assembly and do not bind or 'pack' nucleic acids in their capsid particles (page 67, col. 1).

20. Pumpens does not explicitly teach replacing one or both cysteine residues at positions 48 and 107 by another residue and adding a C-terminal cysteine residue to achieve the stabilizing effect.

21. Zlotnick teaches that the protamine domain (residues 150-183) at C-terminal of HBc is required for packaging viral RNA and deletion of this region results in the generation of HBcΔ virus capsids free of RNA (abstract; pg. 9556, col.1; pg. 9560, col. 2). Zlotnick also teaches that the addition of a single heterologous Cys at C-terminus of HBcΔ can stabilize the virus capsid dimers after deletion of its protamine domain 150-183. Zlotnick shows that the Cp*150 capsids, in which three native Cys48, Cys61 and Cys107 are replaced by three Ala, and a single heterologous Cys is added to position 150 after deletion of its protamine domain 150-183, forms disulfide dimers at pH 7.5 and 9, but not Cys-free Cp*149 (see Figure 2, right column 9557). Zlotnick has shown that unlike the Cys-free Cp*149 capsids, the Cp*150 capsids, is more stable

than not Cys-free Cp*149, and can resistant to dissociation by 3.5 M Urea, suggesting that disulfide bond formation by Cp*150 can promote capsid assembly (Results and Discussion, paragraph 1 and 2, p. 9558).

22. Zheng teaches the function of native cysteines in formation of HBc particles. Zheng teaches that the intra-chain disulfide bonds are not essential for core particle formation, but inter-chain disulfide bonds are involved in formation of HBc capsid dimers with the identical residues of another monomer. Zheng teaches that the native Cys107 is buried within the particle structure and is not involved in HBc capsid formation. The native Cys61 and Cys183 are always, and Cys48 is partially, involved in inter-chain disulfide bonds with the identical residues of another monomer.

23. It would have been obvious to one of ordinary skill in the art to make a C-terminal truncated HBcΔ chimera containing an epitope at its N-terminal, immunodominant loop, or C terminal region, or containing two epitopes is these areas, in which native Cys48 and/or Cys107 are conservatively replaced by another residue, and a heterolgous Cys is added at C-terminal of HBcΔ. One of ordinary skill in the art would have been motivated to do so and would have reasonable expectation of success that such HBcΔ chimera would be capable of incorporating foreign epitops, and free of viral nucleic acid binding and with enhanced stability, given the knowledge HBcΔ chimeras are free of viral RNA, while still capable of self-assembly as taught by Zlotnick, and a various of HBcΔ chimera containing an epitope(s) at its N-terminal, immunodominant loop, or/and C-terminal region have been successfully made as taught by Pumpens, given the knowledge that the addition of a heterologous cysteine residue to an HBcΔ C-terminal truncation results in dimer formation and enhanced stability, as taught by Zlotnick,

and also given the knowledge that native Cys48 and Cys107 are not essential for HBc dimer formation, as taught by Zhang. Thus the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

24. Claims 1-6, 8-28, and 30-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Page, et al (WO 01/98333 A2), Birkett (6,231,864), both in view of Zhang (1992, J. Biological Chemistry, Vol. 267 (13): pp. 9922-9429).

25. Claims 1-6, 8-14, 16-28, 30-42 and 46 are summarized above. Moreover, the said HBc chimer contains a heterologous linker residue for a conjugated epitope present in the HBc immunodominant loop between amino acid residues 76 and 85 (Claims 43-45).

26. Page teaches the use of HBcΔ as a vehicle for the presentation of epitopes. Page teaches modified HBcΔ chimer where one or more of the four arginine repeats responsible for RNA binding at c-terminal (between 150-180) have been deleted followed by the addition/retention of a C-terminal cysteine residue. Page teaches "[t]he removal of the arginine repeats residues the binding of nucleic acid, whilst retention of the C-terminal cysteine allows for the formation of a disulphide bond which in the native structure is important for the formation of a stable particle." (See page 2). Page teaches the addition of epitopes at the C-terminus, in and around the e1 loop from roughly residues 68 to 90 (i.e. the immunodominant loop) and the N-terminus (See page 10). The epitopes may be B-cell epitopes or T-cell epitopes (See pages 11 and 26). The recombinant core antigen may contain multiple heterologous epitopes. (See pages 11 and 26) Moreover, these epitopes may be different epitopes from the same organism or even multiple copies of the same epitope within the core molecule. Epitopes may be conformational or linear.

Epitopes may range widely in size, which would correspondingly affect the overall size of the chimer. Page teaches that the protein self-assembles into particles which may closely resemble the particles formed by native HBcAg (See page 9).

27. Page does not explicitly teach incorporating a heterologous linker residue for a conjugated epitope present in the HBc immunodominant loop between amino acid residues 76 and 85 and does not teach replacing one or both cysteine residues at positions 48 and 107 by another residue.

28. Birkett teaches incorporating a heterologous linker residue for a conjugated epitope present in the immunodominant loop of HBc. Birkett teaches introducing a lysine residue at the HBc immunodominant loop between positions 76-85 for a conjugated epitope (whole document, particularly see Abstract, Example 1 and claims).

29. The relevance of Zhang is set forth *supra*.

30. It would have been obvious to one of ordinary skill in the art to make a C-terminal truncated HBcΔ chimera containing an epitope(s) at its N-terminal, immunodominant loop, or/and C-terminal region, wherein a heterologous linker residue for a conjugated epitope is present in the HBc immunodominant loop between amino acid residues 76 and 85, wherein a Cys is added at their C-terminus, and native Cys48 and/or Cys107 are conservatively replaced by another residue. One of ordinary skill in the art would have been motivated to do so and would have reasonable expectation of success, given the knowledge that HBcΔ chimeras are capable of incorporating foreign epitope(s) at their N-terminal, immunodominant loop, or/and C-terminal region, and also capable of forming viral RNA-free capsid, as taught by Page, given the knowledge that addition/retention of C-terminal cysteines allows formation of a stable HBcΔ

dimer particle as taught by Page, given the knowledge that HBc chimera containing a chemically-reactive linker residues for a conjugated hapten at their immunodominant loop have been successfully made as taught by Birkett, and also given the knowledge that native Cys48 and Cys107 are not essential for HBc dimer formation, as taught by Zhang. Thus the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

31. No claims are allowed.

32. Claims 7, 15 and 29 are free of the prior art. Claims 7, 15 and 29 are objected as being dependent from the rejected claims.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bo Peng, Ph.D. whose telephone number is 571-272-5542. The examiner can normally be reached on M-F, 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell, Ph.D. can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Bo Peng, Ph.D.
11/9/06

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